In vivo imaging of fiber pathways of the human brain with ultra-high gradients

Van J Wedeen[1], Lawrence L Wald[1], Julien Cohen-Adad[1], M Dylan Tisdall[1], Jennifer A McNab[1], Ruopeng Wang[1], Thomas Witzel[1], Ralph Kimmlingen[2], Eva Eberlein[2], Philipp Hoecht[3], Boris Keil[1], Juergen Nistler[2], Dietmar Lehne[2], Keith Heberlein[3], Herbert Thein[2], Franz Schmitt[2], Jack Van Horn[4], Arthur Toga[4], and Bruce R Rosen[1]

[1]*A. A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, United States,* [2]*Siemens Healthcare, Erlangen, Germany,* [3]*Siemens Healthcare, Boston, MA, United States,* [4]*Laboratory of Neuro Imaging, Dept. of Neurology, UCLA, Los Angeles, CA, United States*

Introduction. A critical determinant of the sensitivity, accuracy, and resolution of MRI of the fiber pathways of the brain is gradient strength. To push the envelope of diffusion MRI in humans, we developed a new scanner purpose-built for diffusion MRI with ultra-high gradients of *300 mT m*$^{-1}$, more than 3 times stronger than any previously achieved in human subjects. Owing to synergistic effects of gradient strength - reduced TE, increased time-efficiency, and improved structural resolution with reduced diffusion time - this technology, along with more efficient data collection schemes, was expected to yield gains in sensitivity and resolution of white matter imaging and MRI tractography of 5-10 fold over previous technology, and to make it possible to image in human subjects basic aspects of whole-brain structure previously demonstrated only in non-human tissue specimens.

Methods. Diffusion spectrum MRI (DSI) was obtained in normal human subjects at multiple maximum diffusion b-values and maximum gradient strengths, b_{max} and G_{max}, reconstructed with streamline tractography, and compared. The scanner, the Siemens 3T Connectom, is a 3T Skyra scanner augmented by a unique gradient subsystem. The Connectom (AS302†) gradient system capable of up to *300 mT m*$^{-1}$ and slew rate of 200 *mT m*$^{-1}$ *ms*$^{-1}$. The slew rate was de-rated during the diffusion encoding to prevent physiological stimulation. The RF system included a body transmit coil and a close-fitting 64 channel head receive array. As a precaution against gradient-induced magnetophosphenes, isocenter was landmarked between the eyes and test scans performed in each subject with gradients stepped from to the peak value of *300 mT m*$^{-1}$ in each axis; no visual or other stimulation was experienced by any subject.

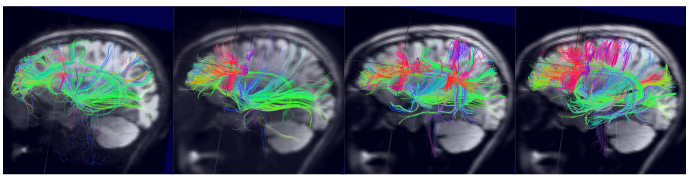
For each subject, registered DSI's were acquired with sensitivities b_{max} *10,000 s mm*$^{-2}$ with four maximum gradient amplitudes: G_{max} = *40 mT m*$^{-1}$ (representative of conventional 3T scanners), *100 mT m*$^{-1}$ (representative of recent state-of-the-art instruments), and ultra-high gradients of *200 and 300 mT m*$^{-1}$. Further scans were obtained with b_{max} *5,000 s mm*$^{-2}$ with G_{max} *40 mT m*$^{-1}$ and *15,000 s mm*$^{-2}$ with *300 mT m*$^{-1}$.

DSI acquisition used a spin-echo EPI pulse sequence with symmetric diffusion-encoding gradient lobes (to preclude quadratic phase terms from Maxwell fields), with minimum diffusion time $\delta + \Delta$ and TE for each scan. DSI diffusion encoding used 257 gradient values forming a 3D cubic lattice covering a hemisphere of q-space. All acquisitions used a constant TR = 3s, or 13 min per scan. The acquisition matrix was a para-median sagittal slab with isotropic resolution of 2.3 mm isotropic EPI with 20-40 slices using an in-plane acceleration of R=3 (using GRAPPA). For b_{max}=15,000, TE= 48ms at G_{max}=300 mT m^{-1} For b_{max}=10,000, TE= 50ms at G_{max}=200 mT m^{-1} . The TE=68ms at G_{max}=200 mT m^{-1} and TE=113ms at G_{max}=40 mT m^{-1} .

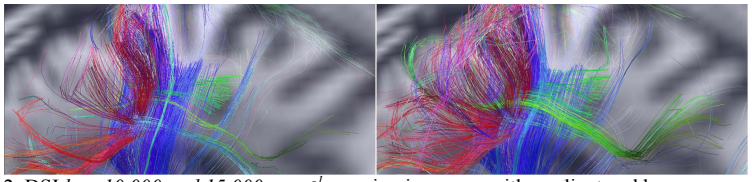
Studies of each subject were co-registered for head motion, reconstructed and tracked with deterministic tractography, and cerebral path structures of interest identified with TrackVis; analysis was performed identically across all the studies in each subject. Structures of interest included well-characterized path crossings including multiple components within the centrum semiovale, sagittal stratum, and of the cingulum bundle, as well as surveys of large simple regions, eg., paths terminus on a chosen slice. Studies were compared for their ability to image known pathways and uncontroverted path crossings.

Results. 1. Effect of gradient strength on diffusion MRI of path crossings. DSI with peak gradients G_{max} *40, 100, 200, and 300 mT m*$^{-1}$, with mixing time adjusted for constant at constant b_{max} *10,000 s mm*$^{-1}$ are shown in Fig 1, panels 1-3 (from left to right), and b_{max} *15,000* in panel 4. As noted, TE's are minimized to represent more realistic conditions. The total numbers of path solutions identified within SLF (horizontal green, at center) increases by about 50% from the conventional (*40 mT m*$^{-1}$) to ultra-high gradient levels. Crossing pathways increase more dramatically, their count increasing by 2-3x from conventional to intermediate gradient performance (*100 mT m*$^{-1}$), and an additional 2-3x gain from intermediate to the ultra-high gradient (*100 vs 300 mT m*$^{-1}$). Note at *40 mT m*$^{-1}$ (panel 1) that the scarcity of callosal pathways (red) interacting with SLF seems inconsistent with known anatomy. Analysis of paths terminating in each slice shows similar increases in intra-cortical radial paths with increasing peak gradient amplitude.

2. Specific effect of gradient strength on diffusion contrast at ultrahigh gradients. In Fig 2, crossings of callosal pathways (red) are compared for DSI with G_{max} *200* vs. *300 mT m*$^{-1}$ and b_{max} *10,000* and *15,000 s mm*$^{-2}$, respectively. Having nearly equal TE's of 52 and 48 ms, the difference between these studies is almost entirely due to gradient strength. At equal intrinsic SNR, increasing the gradient amplitude and b-value yields improved detection of callosal fibers (red, center), and of the crossing paths of the superior longitudinal fasciculus (green; top center) and the cortocspinal tract (blue), which form a grid. This gain was typical across >10 well-characterized structures.



1. Increasing DSI gradient improves fiber structure.



2. DSI b_{max} *10,000 and 15,000 s mm*$^{-1}$ crossing increases with gradient and b.

Discussion. Ultra-high gradients yield substantial and immediate gains in the sensitivity, accuracy and resolution of diffusion tractography, as defined by identification of known structure and fiber crossing, in the human brain. It is striking that imaging gains in image are still demonstrated between two ultrahigh gradient values, independent of the benefit of a befit in signal-to-noise. Diffusion tractography with ultra-high gradients yields many-fold improvements in image quality, and demonstrates basic qualitative features of cerebral fiber architecture, including the pervasive and orderly character of path crossings, and the pervasive radial orientation of intracortical structure, previously known only from fixed tissue for the first time in living human subjects.

†*Work in Progress. The information about this product is preliminary. The product is under development and is not commercially available in the U.S. and its future availability cannot be assured.*

Acknowledgments*: This work was supported by the Human Connectome Project 5U01MH093765-02, NIH MH 5R01MH064044-07, P41 RR023953, and NSF Biological Physics 0855161.*